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Selected Topics in Toxicological Pathology

A. **Metals**

1. Lead

Sources - until 1979 additive to gasoline (>725,000 tons/year), **lead based paint** (still in older buildings-pre 1940), batteries

1). Following the removal of lead from **gasoline** the blood levels of lead in the US population dropped from 12.2ug/dL in 1980 to 3.2ug/dL in 1991 and has continued to fall since.

2). In poor urban areas as many as 20% of black children under 5 years still have elevated blood levels (i.e., >5ug/dL/d)

3). Industrial workers manufacturing **batteries** and other products containing lead may have elevated levels

4). Some **food products** may be contaminated with lead; in mid 90s some imported candies (Mexico) and food coloring (Iraq) was found to contain high lead levels.

b. Clinical and pathology- effects usually from long term exposure rather than from rapid ingestion of large quantities(See Robbins Figure 10-9, page 422)

1). **Anemia** - enzymatic inhibition of hemoglobin synthetic pathway leads to chelation of iron to protophorphryin

a). Increased serum free RBC protophorphyrin, urinary coprophyrin III and gamma-aminolevulinic acid

b). RBCs - hypochromia from decreased hemoglobin and basophilic stippling from impaired RNA degradation

2). Nervous system - **impaired mental development** in children, footdrop and wristdrop in adults with progression to convulsions, coma and death. Levels above 100ug/dL usually seen in encephalopathy though lower levels may also produce neurologic symptoms

a). Neuronal necrosis, edema, demyelination of white matter, reactive astrocytosis

b). Peripheral motor nerve **demyelination**

3). Kidney - aminoaciduria and glycosuria from tubular injury with **intranuclear inclusions** of lead/protein

4). GI tract - **colicky abdominal pain** with vomiting and constipation from smooth muscle contractions

5). Bone and teeth - deposition of lead in gums **(blue line)** and at epiphysial region of growing bones

c. Diagnosis - **elevated erythrocyte protoporphyrin** level of 10-19ug/dL is "mild lead poisoning", 20-24ug/dL should be investigated to remove the patient from the lead source, and >25ug/dL should be treated as below

Treatment - dimercarprol (BAL) and edetate calcium disodium (EDTA) - chelating agents

Government programs - see epa.gov/opptintr/lead/

2. Mercury

Sources - **industrial waste product**, but also in antiseptics, diuretics, latex paints (until 1991), **thermometers**, batteries, dental amalgams

Clinical and pathology -

1). Acute poisoning from ingestion (as suicide attempt) or inhalation of vapor in industry - produced **acute tubular necrosis of kidneys** and ulcerations of GI tract

2). Chronic exposure

a). Symptoms -dementia , emotional instability, visual and auditory problems

b). Pathology - Neuronal loss in cerebrum and cerebellum, renal glomerular changes

c). Can test for chronic exposure (and amount) with **hair sampling** since mercury is deposited in hair at a level related to serum levels at the time of growth.

3. Arsenic

Sources - Primarily in **pesticides** - binds to sulfhydryl groups of Enzymes - also occurs **naturally in soil** and can leach into drinking water

Clinical and Pathology

1). Acute poisoning - usually from suicidal attempt - rapid respiratory death with severe abdominal pain and renal tubular necrosis

2). Chronic - accumulates in hair, skin and nails, and is excreted in urine.

a). Skin changes include increased pigmentation with focal thickening due to increased keratin- arsenical keratosis

b). Epidermal dysplasia may lead to squamous cell carcinoma

c). Nails develop ridges (Mees' lines)

d). Neuropathy from peripheral nerve demyelination

e). Hepatic angiosarcoma in adults

B. Ethyl alcohol abuse

Fetal alcohol syndrome

a. Incidence - varies from 1 out of 1,500 to 1 out of 600 live births (totaling from 2-12,000 cases/year in the US. **(Fetal Alcohol Effects - 1 in 300: FAS children born to alcoholic women - 1 in 10).**

1). Related to differences in drinking practices.

2). **A pregnant woman who drinks any amount of alcohol is at risk, since a "safe" level of alcohol ingestion during pregnancy has not been established.** Currently about 15% of women drink alcohol during their pregnancy

3). Congenital anomalies (both major and minor) are seen in 9% of infants of mothers who consume less than one alcoholic drink during early pregnancy.

4). When alcohol consumption is 1-5 drinks per month during early pregnancy, the incidence is 14%.

5). With heavy drinkers with an average daily ingestion of 45ml absolute alcohol, the incidence rises to 32%.

b. Clinical features and pathology

1). **Intrauterine growth retardation**: growth deficiency in the fetus and newborn in all parameters head circumference, weight, height)

2). Delayed development with **decreased mental functioning** (mild to severe - IQ of 50-85)

3). **Facial abnormalities** including small head (microcephaly); small maxilla (upper jaw); short, up-turned nose; smooth philtrum (groove in upper lip); smooth and thin upper lip; and narrow, small, and unusual-appearing eyes with prominent epicanthal folds

4). **Heart defects** such as ventricular septal defect (VSD) or atrial septal defect (ASD)

5). Limb abnormalities of joints, hands, feet, fingers, and toes.

c. Treatment - management only of infant with syndrome

Chronic alcoholism

Chronic alcoholic liver disease
Chronic pancreatitis
Alcoholic cardiomyopathy
Peripheral neuropathy
Associated malnutrition

C. Insecticides and herbicides (see Robbins Table 10-13, page 423)

Organophosphates (Parathion, Diazinon, Malathion)

Sources - **insecticides and nerve gases**

Irreversible inhibitors of cholinesterases - results in abnormal transmission at peripheral and central nerve endings. Absorbed through skin, lungs and GI tract producing **neurotoxicity** (acutely - pupillary constriction, blurring of vision, muscular paralysis, diarrhea, abdominal cramps, salivation and bronchconstriction) and **delayed neuropathy**

Long term effects - neuromuscular damage

Treatment - **antidote is pralidoxime** which reactivates the enzyme by removing the phosphate group. Relieve symptoms with atropine

Chlorinated hydrocarbons (DDT, chlordane, Methoxychor, Lindane)

Sources - **insecticides**

Acute ingestion of large doses causes **neurologic effects** with delirium and convulsions leading to coma and death.

Chronic exposure leads to hepatic accumulation with fatty change.

Paraquat - **herbicide**

a. Acute illness - few days following ingestion - ulceration of oral mucosa, necrosis of liver, renal tubular necrosis, **diffuse alveolar damage** of lungs with edema, hyaline membrane formation and hemorrhage. Pulmonary fibrosis may follow with high mortality rate.

D. **Industrial chemicals**

Methyl alcohol (methanol - wood alcohol)

Source - **widely used solvent**; added to laboratory grade ethanol to deter consumption by rendering it "nonpotable"'

Highly toxic - **20mLmay be fatal** - metabolized to formaldehyde and formic acid which are toxic and produce **metabolic acidosis**

In low doses effects retina and optic nerve with irreversible damage leading to blindness. Higher doses produce neurotoxic effects and death

Treatment - **ethanol** to preferentially tie up alcohol dehydrogenase and allow excretion of methyl alcohol without its being metabolized

Ethylene glycol

Source - **antifreeze** products

Toxic in small doses and lethal at ingestion amounts of 100mL. Metabolized by alcohol dehydrogenase to glyoxylic and oxalic acids.

Produces **metabolic acidosis**, decreased renal blood flow and **renal failure** with deposition of calcium oxalate crystal in tubules

Treatment - **ethanol** to preferentially tie up alcohol dehydrogenase and allow time for hemodialysis and forced diuresis of ethylene glycol without its being metabolized

Carbon monoxide

Sources **- automobile fumes**, natural gas, coal burning, improper combustion in household gas and paraffin heaters

Combines with hemoglobin to form **carboxyhemoglobin,** which cannot carry oxygen. High affinity of CO for Hb (200X that of oxygen) quickly depletes oxygen-carrying capacity of blood

Symptoms appear when 20% of Hb has been converted to carboxyhemoglobin and **death occurs at 50-60% CO-Hb** in a healthy person and at much lower levels in people with cardiovascular or pulmonary disease.

Symptoms start with headache and confusion then progress to visual disturbances, dizziness, convulsions and coma.

Pathology includes **cherry red color of skin**, blood, and internal organs, especially lung. Cerebral edema present; survivors may show necrosis of globus pallidus

Cyanide

Source - **fruits** (seeds of peaches and apricots), **drugs** (Laetrile), **industry** (mining, electroplating)

Highly lethal at dose of 0.1mg.

Cyanide combines with and inactivates cytochrome oxidase, blocking cellular energy production and causing rapid death form failure of cellular oxidative and respiratory processes.

Pathology - tissues may be **"cherry-red"** in manner similar to carbon monoxide poisoning.

E. **Therapeutic agents**

Aspirin

Source - widely used in over-the-counter medications

Salicylates directly stimulate the respiratory center producing an initial respiratory alkalosis then (through overwhelming of acid-buffering capacity of circulation), a metabolic acidosis.

Clinical symptoms - tinnitus, sudden deafness, hyperpnea, vomiting, progressive lethargy

Treatment - with acute ingestion, plasma salicylate levels should be measured 6 hours after ingestion and plotted on a nomogram to determine potential severity of disease - this is not helpful in chronic ingestion. Depending on levels and clinical symptoms treatment may consist of activated charcoal, emesis, and correction of dehydration and electrolyte losses.

Pathology - aspirin may cause

1). gastric ulcers with hemorrhage

2). bleeding from altered platelet function

3). acute fatty change of the liver with liver failure and encephalopathy when associated with Reye's syndrome (following aspirin use in young children with viral infections such as chicken pox and influenza).

Acetaminophen

Dose related disease - in nonalcohol users, severe disease is usually associated with an intake of 10-15 grams. (Therapeutic doses may be up to 4 grams/day). In heavy alcohol users (not necessarily alcoholics) a dose of 4-6 grams/day (just over the therapeutic level) may be associated with mild to severe liver disease.

Clinical phases

1). Hours after ingestion - nausea and vomiting lasting for hours to one or two days

2). Few symptoms - feeling of well being for one or two days

3). Return of GI symptoms along with painful liver followed by progressive jaundice, hypoglycemia and increased PT. Can lead to hepatic encephalopathy, hepatorenal syndrome, bleeding diathesis or death from hepatic failure.

Action - overwhelms normal metabolic pathways of liver and produces toxic intermediates leading to hepatocyte cell death

Laboratory features - initial small then large rise in AST, ALT and bilirubin. With massive hepatic cell death, the AST and ALT may return to near normal levels before the death of the patient from liver failure

Treatment - in early diagnosed cases (within 8 hours of ingestion) N-acetylcysteine is a specific antidote, but is ineffective after 16 hours. Transplantation may be only recourse in severe intoxication with liver failure

F. **Ionizing radiation**

Definitions- see Robbins, page 425

Roentgen - unit of charge produced by x-rays or gamma rays that ionize a specific volume of air

Rad - dose of radiation that will produce absorption of 100 ergs of energy per gram of tissue; 1gm tissue exposed to 1 roentgen of gamma ray = 93 ergs

Gray (Gy) - dose of radiation that will produce absorption of 1 joule of energy per kilogram of tissue; 1Gy=100rad

Rem - dose of radiation that causes a biologic effect equivalent to 1 rad of x-rays or gamma rays

Sievert (Sv) - dose of radiation that causes a biologic effect equivalent to 1 Gy of x-

rays or gamma rays; 1 SV=100rem

Cellular mechanisms

<.5Gy = no effect, 1-2 Gy = killing of proliferating cells, >10Gy = overt necrosis

Changes - low dose produces injury of DNA which may be repaired; if DNA damage is extensive, apoptosis occurs; delayed effects of injury include mutations, genetic instability and chromosomal aberrations

Damage to endothelial cells may lead to delayed vascular insufficiency of tissues

Acute injury

Clinical features- Robbins Table 10-17, page 427

Dose-rem	Category	Symptoms	Prognosis
<200	Subclinical	Mild nausea and vomiting Lymphocytes <1500/m3	100% survival
200-600	Hematopoietic	Intermittent n&v Petechiae, hemorrhage Max PMN & plt depression in 2 weeks, Lymphs <1000/m3	Infections, may need bone marrow transplant
600-1000	GI	N & v, diarrhea Hem and infection in 1-3 wks Severe PMN and plt depression	Shock and death in 10-14 days even with replacement therapy Death in 14-36 hours
>1000	CNS	Lymphs <500/m3 Intractable n&v, confusion, somnolence, convulsions Coma in 15 min-3 hour Lymphs = 0	

Delayed injury - Robbins Table 10-16, page 426

Organ	**Complication**
Bone Marrow	Hypoplasia, leukemia
Skin	Atrophy of epidermis and fibrosis of dermis
Heart	Interstitial fibrosis
Lung	Interstitial and intra-alveolar fibrosis
GI tract	Ulcers, fibrosis, strictures, adhesions
Liver	Cirrhosis
Kidney	Cortical atrophy, interstitial fibrosis
Urinary	Submucosal fibrosis
Brain	Necrosis of white matter, gliosis
Testes	Tubular atrophy
Ovary	Stromal fibrosis
Thyroid	Hypothyroidism
Breast	Fibrosis
Thymus, LN	*Lymphoma*